REMARKS

Claims 2, 3, 8-10, 16-37, and 40-51 are pending. Applicants acknowledge that the restriction requirement has been deemed final. Accordingly, claims 2, 3, and 22-37 are withdrawn from further consideration as being drawn to a non-elected invention. Claims 2, 3, 10, 18-37, 40-43, and 51 are canceled herein without prejudice. Claims 8, 9, 16, 17, and 44-50 are amended herein to more clearly set forth aspects of the invention. New claims 52-54 are presented herein. Accordingly, claims 8, 9, 16, 17, and 44-50, as amended, and new claims 52-54 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for amendments to claim 8 is found in original claim 11, wherein support for the phrase "inhibits tryptase with a Ki of less than 1 x 10^{-6} M" is found; in original claims 4 and 6, and at page 2, line 27 through to page 3, line 6, at page 14, lines 4-16, and in Figure 3, wherein support for a recombinant protein that has tryptase inhibitory activity and is homologous to SEQ ID NO: 2 as defined by 80% or more of the amino acids in the sequence being completely conserved as identical residues if the protein is aligned with the sequence of SEQ ID NO: 2, the alignments being obtained using GCG's bestfit command (gap creation penalty = 2.5; gap extension penalty = 0.5) is found; and in the Sequence Listing and Figure 1, wherein an amino acid sequence of SEQ ID NO: 2 is presented. Support for amendments to claims 9, 16, and 17 is found in original claims 9, 16, and 17. Support for amendments to claim 44 is found, for example, in the Sequence Listing and Figure 1, wherein an amino acid sequence of SEQ ID NO: 2 is presented. Support for amendments to claims 45-50 is found in previously presented claims 45-50. No issue of new matter is introduced by these amendments.

Support for new claims 52-54 is found throughout the specification and in the original claims. Specifically, support for new claim 52 is found in original claim 11, wherein support for a recombinant protein or protein fragment that inhibits tryptase with a Ki of less than 1 x 10^{-6}M is found; and in the Sequence Listing and Figure 1, wherein an amino acid sequence of SEQ ID NO: 2 is presented. Support for new claims 53 and 54 is found, for example, in original claims 4 and 6, and at page 2, line 27 through to page 3, line 6, at page 14, lines 4-16, in Figure 3, and at

page 4, lines 9-14, wherein support for a recombinant protein that has tryptase inhibitory activity and is homologous to SEQ ID NO: 2 as defined by 90% or 95% or more (i.e., 80% or more) of the amino acids in the sequence being identical to amino acid sequences of SEQ ID NO: 2, wherein the sequence alignment is determined using GCG's bestfit command (gap creation penalty = 2.5; gap extension penalty = 0.5) is found. No issue of new matter is introduced by these amendments.

In the response to the restriction requirement filed August 2, 2004, Applicants' inadvertently introduced a clerical error into claim 9 whereby the word "mast", as it appeared in original claim 9, was replaced by the word "mass". This mistake was the result of a typographical error and Applicants bring this issue to the Examiner's attention to clarify the record. This typographical error has been corrected to revert to the word "mast" as originally presented in original claim 9. Thus, no issue of new matter is hereby introduced.

Amendment to the Specification

In accordance with the Examiner's suggestion, a new title of the invention is submitted herewith which Applicants believe to be more clearly indicative of the claimed invention.

Rejections under 35 USC § 112

Claims 16-21 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 18-21 are canceled herein, thereby obviating any rejection of these claims. Claims 16 and 17 are amended to delete dependency to canceled claim 1. Applicants, therefore, believe that the amendments to claims 16 and 17 are curative of the rejection and respectfully request that the Examiner withdraw the rejection of claims 16 and 17 under 35 U.S.C. §112, second paragraph.

Claims 8-10, 16-21, and 40-51 stand rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. Claims 10, 18-21, 40-43, and 51 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and Applicants' arguments hereinbelow, the rejection, as it applied to claims 8-9, 16-17, and 44-50, is respectfully traversed.

The Examiner acknowledges that the specification is enabling with respect to a protease inhibitor protein of SEQ ID NO: 2. Applicants decidedly disagree, however, with the Examiner's comments pertaining to an alleged lack of teaching presented in the specification that would enable a skilled artisan to make active fragments of SEQ ID NO: 2 that would exhibit the recited functional characteristics of the full length SEQ ID NO: 2. Generating protein fragments is a matter of routine practice in laboratories versed in molecular biology and/or protein chemistry. Moreover, a skilled practitioner having read the specification would appreciate which amino acid residues/regions of SEQ ID NO: 2 are likely to be structurally and functionally significant because Figure 3 presents an amino acid sequence alignment of SEQ ID NO: 2 (TdPI) with Kunitz domains of several known and related Kunitz-type protease inhibitors. See also page 3, lines 11-14. Indeed, a skilled molecular biologist familiar with the literature relating to the family of Kunitz-type protease inhibitors which was available at the filing date of the present application would have seen numerous alignments of this family of proteins and would have considered it trivial to perform additional alignment analyses.

Readily available software also enables a skilled practitioner to analyze primary amino acid sequences (e.g., SEQ ID NO: 2) and predict with reasonable accuracy, the three-dimensional structure of a protein based only on the amino acid sequence. Computer modeling, as described above, is particularly well applied under circumstances wherein a protein belongs to a well-characterized family of proteins for which sequence and structural information is readily available. Applicants submit for the Examiner's consideration Exhibits A-C (Abstracts only for Xu et al. J Mol Biol 276:955, 1998; Zhang et al. J Mol Biol 285:2089, February 1999; and Qasim et al. Biochemistry 38:7142, June 1999) which present evidence that detailed structural information was available for members of the Kunitz-type protease inhibitor family prior to the earliest priority date to which the present application is entitled. In combination, sequence alignments and predicted structural information, which is reinforced by empirically determined

structural information pertaining to related family members, contribute critical information that enables skilled practitioners to predict accurately, and with a reasonable expectation of success, functional domains and critical residues therein for essentially any protein.

Applicants, therefore, submit that generating active fragments of SEQ ID NO: 2 would be well within the capabilities of an ordinarily skilled artisan because the specification and the available literature present sufficient guidance to direct the artisan to delineate functional domains of SEQ ID NO: 2. Moreover, once generated, it would be a matter of routine experimentation to test such fragments for the recited activity using the protease inhibition assays described in the specification at, for example, page 15, line 1 through to page 16, line 24. Only those fragments that satisfy the sequence requirements of the claims and inhibit tryptase at the recited level fall within the scope of the claims. In view of the above, Applicants assert that the specification is enabling for the claimed active fragments of SEQ ID NO: 2.

Applicants also assert that the specification is enabled for a recombinant protein derived from a blood-feeding arthropod ectoparasite or an active fragment thereof that inhibits tryptase with a Ki of less than 1×10^{-6} M; and exhibits significant sequence homology with SEQ ID NO: 2 or an active fragment thereof, wherein said sequence homology is defined as 80% or more (e.g., 90% or 95%) of the amino acids in the sequence being completely conserved as identical residues if the recombinant protein is aligned with the sequence of SEQ ID NO: 2 using GCG's bestfit command (gap creation penalty = 2.5; gap extension penalty = 0.5). As described in detail herein above, the teachings of the specification, in combination with common knowledge at the priority date, present guidance on which basis a skilled practitioner could isolate and test the claimed recombinant protein or active fragment thereof having the recited properties. Only those recombinant proteins that satisfy the sequence requirements of the claims and inhibit tryptase at the required level fall within the scope of the claims. Proteins that satisfy the sequence requirements of the claims but not the functional requirements are not embraced by any of the claims. The specification teaches the skilled person how to determine whether a candidate protein meets the sequence requirements of the claim and provides detailed information on tryptase inhibition assays to determine if a protein meets the functional requirements of the claim. See page 15, line 1 through to page 16, line 24. Accordingly, information presented in

the specification, supplemented by common knowledge relating to procedures routinely performed by skilled practitioners, enables such artisans to identify recombinant proteins that fall within the scope of the claims.

In view of the above, Applicants assert that the Examiner's statement that "... the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity *over the full length of SEQ ID NO: 2* to *share the same function* as the polypeptide of SEQ ID NO: 2." is unduly limiting and without basis either with respect to scientific premise or the law.

The references on which the Examiner relies to support arguments set forth in the Office Action have been considered, but Applicants believe that none of these references is particularly relevant to the presently claimed invention for the reasons stated herein below. Mikayama et al. (PNAS 90:10056, 1993) is directed to the molecular cloning and functional expression of a cDNA encoding glycosylation-inhibiting factor (GIF). The Examiner's attention is directed to page 10060, right column, lines 6-11, wherein the authors indicate that there is some uncertainty as to whether or not a single amino acid difference between GIF and macrophage migratory inhibitory factor accounts for their differing biological activities. Moreover, Applicants assert that it is not proper to apply the findings of a single reference directed to a **specific** protein broadly to **all** proteins, and it is particularly misleading to apply the findings to an unrelated protein such as TdPI.

Burgess et al. (J Cell Biol 111:2129, 1990) describe site directed mutagenesis of lysine 132 (not 118 as indicated by the Examiner) to glutamic acid in heparin-binding (acidic fibroblast) growth factor-1 (HBGF1). The expressed mutant protein had substantially reduced biologic activity as compared to the wildtype (unmutated) HBGF-1. In that lysine 132 had been previously implicated "as being important to the heparin-binding, receptor-binding, and mitogenic activities of HBGF-1" (See Abstract), a skilled artisan would have predicted a reduction in activity resulting from the introduction of such a mutation into HBGF-1. Indeed, the intent of the authors appears to have been to generate a mutant having altered (i.e., reduced) HBGF-1 functional activity. Thus, a skilled artisan would understand that such an approach would be contraindicated if one wanted to generated an active variant, for example, of HBGF-1. The Burgess et al. reference is, therefore, not relevant to the claimed invention, which is directed

to making polypeptides that retain the recited functional properties of SEQ ID NO: 2.

The Lazar et al. reference (Mol Cell Biol 8:1247, 1988) is directed to introducing mutations at residues Asp-47 and Leu-48 of TGF-α. It is noteworthy that these two amino acids are highly conserved in the EGF-like family of peptides. See page 1247, left column, third paragraph, lines 12-16. As indicated herein above with respect to the Burgess et al. reference, a skilled practitioner would not mutate residues that are known to be conserved in a family of related proteins if the intention is to generate a polypeptide that possesses biologic activity of the unmutated protein.

The references authored by Attwood (Science 290:471, 2000) and Skolnick et al. (Trends in Biotech. 18:34, 2000) relate to genome wide sequence analysis and functional annotation of newly identified nucleic acid sequences. Pitfalls of such functional annotation in the absence of additional corroborative data are emphasized in these references. Applicants assert that these references have little bearing on the present invention. This assertion is underscored by the teaching and guidance presented in the specification which sets forth the primary amino acid sequence of TdPI (SEQ ID NO: 2) and other related Kunitz-type protease inhibitor family members and a sequence alignment of the Kunitz-type domains of these related proteins, identifies and characterizes biological functions possessed by TdPI, and indicates critical residues implicated in TdPI biologic activity. The available information pertaining to this family of related proteins, therefore, renders molecular analyses of these proteins highly advanced as compared, in particular, to any analyses that may be performed on newly characterized sequences for which only limited or no sequence homology can be established to known genes/proteins and for which no biologic activity has been experimentally determined.

The Metzler et al. reference (Nature Structural Biol 4:527, 1997) is directed to introducing mutations into CTLA-4 at residues which are known to be conserved in the CTLA-4 /CD28 family. See Abstract. As indicated herein above, a skilled practitioner would not mutate residues that are known to be conserved in a family of related proteins if the intention is to generate a polypeptide that possesses biologic activity of the unmutated protein.

The Examiner has cited Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495, 1994 as supportive that the relationship between the sequence of a

peptide and it's tertiary structure was not well understood and was not predictable. As detailed in the specification and herein, the field of computer-assisted or *in silico* analyses of amino acid sequences has advanced exponentially since this rather antiquated references was published. Applicants, therefore, assert that the state of the present art is not well reflected in the commentary of a reference that is ten years old. Moreover, as stated herein above, extensive structural information was available for related family members at the priority date of the present application that could readily have been extrapolated to predict the structure of TdPI (SEQ ID NO: 2) with reasonable accuracy.

In that claims 18-21 directed to the development of pharmaceutical compositions and/or vaccines have been canceled, Examiner's remarks pertaining to U.S. Patent No. 6,248,329 and Plotkin et al. [(eds) published by W.B. Sunders Company (Philadelphia), 1988] have been rendered moot.

In summary, Applicants assert that the references described herein above are not germane to the presently claimed invention.

In view of the above, Applicants maintain that the rejection of claims 8-9, 16-17, and 44-50 under 35 U.S.C. §112, first paragraph, is improper and respectfully request that the rejection be withdrawn.

Claims 8-10, 16-21, and 40-51 are rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. Claims 10, 18-21, 40-43, and 51 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and applicants' arguments hereinbelow, the rejection, as it applied to claims 8-9, 16-17, and 44-50, is respectfully traversed.

The Examiner acknowledges that Applicants are in possession of the claimed protease inhibitor protein of SEQ ID NO: 2. Applicants maintain that presentation of the amino acid sequence of SEQ ID NO: 2 in the Sequence Listing and Figure 1 of the specification, in combination with the identification of SEQ ID NO: 2 as a member of the Kunitz-type protease inhibitor family and the sequence alignment of several of these family members (including SEQ

ID NO: 2) in Figure 3, fulfills the descriptive requirements for the presently claimed active fragments of SEQ ID NO: 2 and recombinant proteins or fragments thereof that possess the recited properties. A skilled practitioner would thus consider such recombinant proteins having amino acid sequences of 80%, 90%, or 95% or more identity to amino acid sequences of SEQ ID NO: 2 as determined by sequence alignment using GCG's bestfit command (gap creation penalty = 2.5; gap extension penalty = 0.5) to be amply described in view of the specification and common knowledge in the field. It also follows, in view of arguments presented herein above, that fragments of such recombinant proteins having amino acid sequences of 80%, 90%, or 95% or more identity to amino acid sequences of SEQ ID NO: 2 as determined by sequence alignment using GCG's bestfit command (gap creation penalty = 2.5; gap extension penalty = 0.5) are also properly described.

In view of the above, Applicants maintain that the rejection of claims 8-9, 16-17, and 44-50 under 35 U.S.C. §112, first paragraph, is improper and respectfully request that the rejection be withdrawn.

Fees

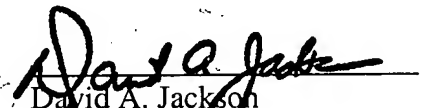
No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited.

In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Petition for a One-Month Extension of Time
Exhibits A-C